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TechNote

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B-TYPE NATRIURETIC PEPTIDE FOR DIAGNOSING CONGESTIVE HEART FAILURE

Request: This TechNote was prepared in response to a request from the Council of Laboratory Leaders on the use of B-type natriuretic peptide in the diagnosis of congestive heart failure. This report focuses on the scientific evidence about the accuracy of B-type natriuretic peptide as a new laboratory blood test to differentiate acute dyspnea caused by congestive heart failure from other conditions such as pneumonia or chronic obstructive pulmonary disease.

BACKGROUND

Congestive heart failure

Congestive heart failure (CHF) is commonly defined as the condition in which an abnormality in cardiac function is responsible for the inability of the heart to pump the quantity of blood required for ordinary activity from a normal filling pressure [1]. Conditions such as increased vascular resistance, damaged cardiac tissue, or malfunctions of heart valves can lead to CHF [2]. The leading cause of CHF is coronary artery disease.

CHF can involve only one side of the heart or both sides. Left ventricular (LV) failure typically occurs first, which causes insufficient circulation to peripheral tissues, and pulmonary edema develops as fluids build up in the lungs. Right ventricular failure results in peripheral edema because blood cannot be pumped toward the lungs for re-oxygenation [2].

Technotes are brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to a formal external review process.

CHF is a progressive disorder and affected patients often require treatment and follow-up [3]. Symptoms of CHF may include fatigue and weakness, exertional dyspnea, orthopnea, paroxysmal nocturnal dyspnea, dyspnea at rest, dyspnea with ordinary physical activity and progress to the inability to carry out any physical activity without discomfort. Other symptoms may include peripheral edema, nocturia, confusion, or impairment of memory. Death in patients with severe CHF occurs either by progressive pump failure or, in as many as one half of all patients, sudden and unexpected death, presumably from an arrhythmia [4].

Dyspnea is the most common symptom in patients with CHF [5]. Dyspnea is reported to be relevant in 2.7% of emergency department (ED) visits and 15% to 25% of all hospital admissions [6].

Epidemiology of CHF

Currently, more than 15 million patients have CHF in North America and Europe, with nearly 1.5 million new cases every year [7]. CHF is the only cardiovascular condition in the United States that is increasing in incidence, prevalence and mortality [3]. This increase is related in part to an aging population and improvements in the diagnosis and treatment of acute myocardial infarction. Survivors of acute myocardial infarction are at a great risk for developing secondary cardiovascular complications, with CHF being common [3]. The severity of CHF and mortality increases with age [8].

In 2001 an estimated 5 million Americans had CHF [9]. CHF affects all age groups, with 550,000 new diagnoses in 2001 [9], and more than 2.5 million hospitalizations each year [10]. The incidence of CHF increases dramatically with age, affecting 2% of persons aged 40 to 59 years, more than 5% of persons aged 60 to 69 years, and 10% of those over 70 years [10]. CHF is the leading cause of hospital admissions in the elderly, accounting for 20% of their total admissions. The 5-year mortality rate for patients with CHF is approximately 50% [11, 12].

CHF affects 1% to 2% of the Canadian population, or 462,000 people [13]. The one-year mortality rates range from 11% in less severe cases to 44% in more severe cases based on the New York Heart Association (NYHA) functional classification. Patients at the most severe stages of CHF (NYHA class III/IV) are estimated to comprise 35% to 45% of the total CHF population [13]. A national survey found that there were a total of 106,130 discharges for 85,679 patients with CHF in the fiscal year 2000/2001 [14]. In terms of total discharges for CHF, 32.7% were readmissions. Total in-hospital mortality was 15.8%. In terms of burden of illness compared with other major illness, CHF is associated with the second highest total number of hospital days and third highest number of patients affected [14].

In Alberta, there are about 5,000 new cases of CHF requiring hospitalization (personal communication, Dr. Justin Ezekowitz, April 2004). From 1994 to 2000, there were 32,139

total hospitalizations for CHF. Among these, 50% (16,162 hospitalizations) were for newly diagnosed CHF [8]. Seniors (age 65 years or older) constituted about 85% of all new diagnoses for CHF. The proportion of hospitalizations for CHF in seniors aged 85 years or older was 13% in 1994/1995 and increased to 18% in 1999/2000.

Diagnosis of CHF

Rapid and accurate diagnosis of CHF is important in the ED so as to initiate the most appropriate treatment to alleviate symptoms and prolong survival [15]. It remains a challenge in clinical practice, however, to differentiate other causes of dyspnea from CHF. Misdiagnosis of CHF by primary care physicians can often range from 25% up to 50% [16]. Misdiagnosis of CHF can be life-threatening because:

- treatments for CHF may be hazardous to patients with other conditions, such as chronic obstructive pulmonary disease (COPD), that may have the same primary symptoms (e.g., dyspnea) at presentation [17, 18];
- it may leave other conditions such as pneumonia untreated; and
- treatments for other causes of dyspnea may similarly be ineffective or hazardous to patients with CHF.

Traditionally, diagnosing CHF has been based on medical history, symptoms, physical examination, electrocardiogram (ECG), chest X-ray, and non-laboratory diagnostic tests to rule out all other causes of dyspnea. Follow-up testing involves echocardiography and exercise stress tests to assess the patient's heart size, shape, and function [19]. Other less widely used tests may include cardiac magnetic resonance imaging or computed tomography and radionuclide ventriculography [20, 21].

Diagnosing CHF can, however, be very difficult, and both under-diagnosis and over-diagnosis are common [22]. The symptoms, signs, and tests mentioned above are neither sufficiently specific nor sensitive for the diagnosis of CHF when each of these variables is viewed independently.

The history, symptoms, and physical examination provide a prior probability that a condition in question is present. This probability can then be modified by the results of a diagnostic test. However, a reliable history may not always be ascertained in an acutely ill patient [18]. In the urgent care setting, it is often difficult to distinguish between cardiac and pulmonary causes of dyspnea [18], especially in elderly patients. The prevalence of both COPD and CHF is high in the elderly, and these two conditions are often present in the same patient [23]. Physical signs, such as elevated jugular venous pressure, a S_3 gallop, pulmonary rales, and edema, are often absent in patients with CHF [18].

The ECG is often altered in patients with LV structural changes. The chest X-ray may detect an enlarged heart and pulmonary congestion. However, 20% of cardiomegaly seen on echocardiography is missed on chest X-ray [11].

Echocardiography provides a rapid, semi-quantitative assessment of the heart wall dimensions and motion, and left ventricular ejection fraction (LVEF) measurement. Echocardiography is considered the gold standard for the detection of LV dysfunction [17] and has become the primary diagnostic tool for CHF today.

While echocardiograms are very useful in diagnosing CHF, they are expensive, costing between $500 to $700 each, have limited availability in an urgent care setting, and do not always reflect an acute condition [6, 17]. Patients with dyspnea may be unable to hold their breath long enough during an echocardiographic study for a good image to be obtained. In addition, technical difficulty due to obesity and lung disease may also impact the quality and accuracy of the echocardiographic image [18, 24]. Echocardiograms are virtually unavailable in rural hospitals in Alberta and diagnosing CHF is mainly based on clinical history and physical exam, chest X-ray, ECG, and lab assessment (personal communication, Dr. Rob Wedel, July 2004).

Echocardiogram may not be helpful to diagnose CHF with preserved systolic function [25]. An estimated 40% to 50% of patients with clinically diagnosed CHF have normal systolic function (i.e., diastolic heart failure) [26]. In these cases, LVEF would be in the normal range on echocardiography. Similarly, many patients with systolic dysfunction have no signs or symptoms [20].

The rapid and accurate differentiation of CHF from other causes of dyspnea remains a clinical challenge, especially in the urgent care setting such as the ED. After evaluating a patient's symptoms, conducting a physical examination, and performing an ECG and chest X-ray, the clinician is often left with considerable diagnostic uncertainty [1, 7]. Therefore, even in large hospitals with readily available echocardiography, using an accurate, sensitive, and specific blood test may provide sufficient pre-test probability to mitigate the need for echocardiography in some patients.

B-TYPE NATRIURETIC PEPTIDE TESTING

Biosynthesis and secretion of natriuretic peptides

The heart is a cardio-respiratory and an endocrine organ. Hemodynamic changes and neurohormonal activation are caused by LV dysfunction. The sympathetic nervous system, renin-angiotensin-aldosterone system, and endothelin pathway are activated to maintain blood pressure and improve perfusion [11, 27].

Natriuretic peptides have two features that distinguish them from other neurohormones: they have beneficial effects in CHF, and they are mainly produced and secreted by the heart [28]. Three types of natriuretic peptides, including A-type, B-type,

and C-type, share a common 17 amino acid ring structure [18]. A-type (atrial) natriuretic peptide (ANP) is secreted primarily by the atrial myocardium [29]. B-type natriuretic peptide (BNP), isolated initially from porcine brain tissue, is a 32-amino acid polypeptide secreted from the cardiac ventricles [30, 31]. C-type natriuretic peptide (CNP) is predominantly secreted from vascular endothelial cells [27, 32-34]. These natriuretic peptides are secreted in response to hemodynamic stress, with higher stress resulting in higher levels of secretion [11].

There is chronic over-stimulation of the renin-angiotensin-aldosterone system in CHF. Sustained increases in norepinephrine and aldosterone produce thickening of the arteries, left ventricular hypertrophy, and a mild degree of chronic myocardial necrosis. The natriuretic peptides are released into the blood as a compensatory mechanism [35]. The most important stimulus for the synthesis of BNP in the heart is an increase in wall stress [28]. The physical actions of the natriuretic peptide system include arterial and venous dilatation, sodium excretion, diuresis, and inhibition of rennin and aldosteron production [36, 37].

BNP is produced in the form of a precursor, pre-pro BNP, which is then cleaved to proBNP and released into the blood, where it is processed into the 32-amino acid biologically active form (BNP) and an inactive metabolite, N-terminal pro-BNP (NT-proBNP) [36]. BNP and NT-pro BNP are reasonably stable, making them good diagnostic markers. BNP and NT-pro BNP are produced in equimolar amounts and assays are commercially available for both entities. There are analytical differences between these compounds in terms of molecular weight, clearance mechanism, and half-life (22 minutes for BNP and 120 minutes for NT-pro BNP) [38] and patient specific differences such as age, gender, renal function, and obesity that affect the blood levels of each [12, 20].

Potential clinical applications

According to the most recent Canadian Cardiovascular Society consensus guidelines [39], the clinical applications of BNP testing include:

- Establishing the diagnosis of CHF;
- Stratifying short and long term prognosis;
- Monitoring for the decompensation of CHF and response to therapy; and
- Screening for LV dysfunction in the general population.

The University HealthSystem Consortium (UHC) in the United States published a *High-Impact Technology Brief* [20] that summarized the clinical evidence on the utility of the BNP test for the four purposes mentioned above. The findings were not presented here because this UHC report did not meet the definition of a systematic review (see Appendix A).

The most established clinical application of BNP is for the detection of cardiac etiologies in patients with dyspnea who present at an urgent care setting and in whom the diagnosis is not readily apparent after clinical evaluation.

Available BNP assays

Setting-up a reliable method for the assay of cardiac natriuretic peptides is very difficult due to the structural, metabolic and physiological characteristics of these hormones [40]. The first widely available BNP test in the United States (US) was a point-of-care fluorescence immunoassay (Triage® BNP test, Biosite Inc., San Diego, Ca), which takes 15 to 20 minutes to perform [20]. Another BNP test was recently developed that can be performed on a completely automated high-throughput (240 tests/hour) analyzer (Advia Centaur® System, Bayer Diagnostics, Tarrytown, NY).

Another commercially available test measures NT-proBNP via electrochemiluminescence on a benchtop analyzer that can be adapted for use in either medium- or high-volume laboratories (Elecsys® proBNP, Roche Diagnostics Corp., Indianapolis, IN). The Roche test is a non-competitive enzyme immunoassay and results are available in 15 to 20 minutes using the analyzer in stat mode. A competitive enzyme immunoassay for NT-proBNP is also commercially available in Europe (NT-proBNP ELISA, Biomedica Grouppe, Austria) [41]. Competitive immunoassays do not require sample pre-treatment, but non-competitive immunoassays may offer advantages of speed, sensitivity, precision, and possibly specificity over competitive immunoassays [41, 42].

A consideration is the difference in assay precision between point-of-care test and those tests performed by auto-analyzer. A multi-centre evaluation study showed that the automated Roche NT-proBNP assay has good analytical performance and better precision than the point-of-care Biosite BNP assay [43].

Range of BNP levels

BNP levels increase with age. For both men and women, over the course of a life time, BNP levels should gradually rise but in general remain less than 50 pg/ml, unless there is the development of LV systolic or diastolic dysfunction [38]. Additionally, women without CHF tend to have somewhat higher BNP values than men of the same age group [44, 45]. There are no significant differences in BNP levels between normal patients with hypertension or diabetes and age-matched controls [45].

The reference ranges for BNP and NT-proBNP vary depending on the assay method employed and the nature of the control population [46]. The cut-off value suggested by the manufacture for the detection of CHF is 100 pg/ml for the BNP point-of-care assay and for the Bayer laboratory-based BNP assay in those aged 55 years or older. In Europe the suggested cut-off values for NT-proBNP are 100 pg/ml for men and 150

pg/ml for women, but 125 pg/ml for both genders in the United States [46]. However, the cut-off values suggested by the manufacturers may not be the best in routine clinical practice. Local cut-off values should be determined in the light of experience of using the test (personal communication, Dr. Martin R. Cowie, April 2004).

Regulatory status

The Triage® point-of-care test received European marketing approval in 1999 and was the first US-marketed BNP test, with initial Food and Drug Administration (FDA) marketing approval in November 2000 [20]. The Roche Elecsys® NT-proBNP test had been on the market in Europe since October 2001 and was approved by the US FDA for marketing in November 2002. The Bayer Advia Centaur® BNP test received FDA approval in June 2003 [20].

Health Canada issued medical devices active licenses for the Triage® BNP test in July 2003, the Elecsys® proBNP in February 2003, and the Advia Centaur® System BNP Assay in January 2004 [47].

No information was located from Health Canada and US FDA websites in respect to the regulatory status of the Biomedica NT-proBNP assay.

Evidence of accuracy of BNP testing for diagnosing CHF

One systematic review [48], one randomized controlled trial (RCT) [49], one international multi-centre trial [17] with four subgroup analyses [50-53], and seven single centre trials [6, 15, 24, 54-57]were located though a comprehensive literature search (see Appendix A for search strategy and selection criteria). These studies evaluated the utility of the BNP/NT-proBNP assays for the diagnosis of CHF in patients presenting with dyspnea. Two study [49, 57] involved patients seen in the setting of general practice, while the other studies included patients presenting at the ED with dyspnea. Since the diagnosis of CHF relies on the clinical judgment of history, symptoms and signs, chest X-rays, echocardiography, and response to treatment [22], all these trials used clinical judgment of all relevant information as the standard reference test. Details of study objectives, participants/settings, manufacture/source and comparison/reference test, and results/conclusions were extracted from each of the primary studies and are presented in Appendix B.

Evidence from systematic reviews

Cardarelli et al. [48] conducted a systematic review to evaluate the potential use of BNP levels as a diagnostic, prognostic, and therapeutic monitoring tool for primary care physicians in both outpatient care and urgent care settings. Because of the scope of this report, only information regarding the diagnostic use of BNP is summarized here.

Three well-designed studies (two were conducted at the ED and one was conducted in the primary care setting) identified by this systematic review showed that a BNP level of 80 pg/ml had sensitivities ranging from 93% to 98% in diagnosing CHF in symptomatic patients, and negative predictive values ranging from 92% to 98%, demonstrating the ability of BNP to rule out CHF.

As the authors pointed out, certain results of included studies need to be interpreted with caution. For example, in two of the studies, the mean BNP concentration in patients with CHF was markedly different: 1076±138 pg/ml in one study [58] compared with 675±450 pg/ml in another study [17]. Moreover, in these two studies the mean BNP levels for patients with baseline LV dysfunction but without CHF were 141±31 mg/ml [58] and 346±390 mg/ml [17], which were considerably higher than the BNP cut-off value of 80 pg/ml that was used to suggest CHF.

The authors concluded that a BNP level of 80 pg/ml is useful in diagnosing CHF in patients with symptoms but without a history of CHF. BNP levels are potentially more useful when a baseline concentration is known for a patient, because BNP levels are increased proportional to the severity of CHF.

Evidence from primary studies

Use of BNP in primary care setting

Two studies [49, 57] assessed the use of the BNP test in patients presenting at the general practitioner (GP)'s office with dyspnea and/or peripheral edema.

In an RCT, Wright et al. [49] reported the ability of the plasma measurement of NT-proBNP to improve the diagnostic accuracy of CHF. Three hundred five patients presenting to their GP with symptoms of dyspnea and/or peripheral edema were randomly assigned to the experimental and control groups. GPs in the experimental group received the results of plasma NT-proBNP measurements to assist with their diagnostic process, while the GPs in the control group did not. The primary end point was the accuracy of the GP's diagnosis compared with that of a panel using the criteria from the European Society of Cardiology Guidelines for the diagnosis of CHF.

The experimental and control groups were comparable at baseline, except that the mean age of the control group was three years older than that of the experimental group. In 305 patients, 77 patients met the panel's criteria for CHF. The sensitivity and specificity were maximized at a cut-off of 100 pmol/l. NT-proBNP measurement (>150 pmol/l) improved the diagnostic accuracy from 49% to 70%, compared to the improvement from 52% to 59% without the NT-proBNP measurement. The main impact of the NT-proBNP assay was that it allowed GPs to rule out CHF.

Nielsen et al. [57] evaluated the utility of NT-proBNP for the detection and exclusion of CHF in a patient population seen in general practice with symptoms of dyspnea for at

least two weeks. The study found that the NT-proBNP levels were significantly higher in patients with CHF alone and in patients with CHF in combination with lung disease than in those patients with dyspnea but without CHF. Correlations between NT-proBNP levels and age and gender of participants were not reported in this study. In this study the predictive characteristics of the NT-proBNP assay were reported separately for males and females over the age of 50 years. The authors suggested that for patients aged 50 years and older, CHF could be ruled out with a high probability if the NT-proBNP level did not exceed 11 pmol/l in men and 17pmol/l in women.

Use of BNP in emergency care setting

Evidence from multi-centre trials

The Breathing Not Properly trial was a large prospective international multi-centre trial designed to investigate the value of the measurement of BNP concentrations for the diagnosis of CHF in patients with dyspnea presenting to EDs [17]. The main findings along with subgroup analyses of the trial were published in several articles [17, 50-53].

The study by Maisel et al. [17] reported the results of rapid measurement of BNP in the emergency diagnosis of CHF in 1586 patients with shortness of breath. The ED physicians, blinded to the results of the BNP test, provided an initial diagnosis and an estimate of the probability of the presence of CHF on a visual analogue scale. Two independent cardiologists, blinded to both the BNP results and the ED physician's diagnosis, determined the final diagnoses based on the review of all relevant clinical information.

BNP levels were significantly higher in patients with CHF compared to that in patients without CHF or in patients with a baseline LV dysfunction but their dyspnea was not caused by CHF. BNP levels alone were more accurate than any other finding from the history, physical examination, or chest X-ray in delineating the cause of dyspnea. BNP values also differed significantly as a function of the severity of CHF but the ranges overlapped. Correlations between BNP level and age or gender of the participants were not reported in this study.

Maisel et al. [50] looked at the impact of age, ethnicity, and gender on BNP decision statistics. They found that BNP levels increased with increasing age, were higher in Caucasians than in Africa Americans, but were not significantly different between males and females. The analysis of receiver operating characteristic (ROC) curves showed that BNP was a stronger predictor in younger patients than in older patients and slightly weaker for female patients than for male patients. An even smaller difference was noted between white and black racial groups.

In a subgroup analysis [51] it was suggested that adding the BNP test to clinical judgment would enhance accuracy from 74% to 81% ($p<.0001$) in determining the correct diagnosis (CHF versus no CHF).

The use of BNP in identifying CHF in patients with a history of asthma or COPD but without a previous history of CHF was presented in another subgroup analysis [52]. About 20% of these patients were found to have CHF as the final adjudicated diagnosis. BNP levels were significantly higher in patients with CHF when compared to the levels in patients without CHF. However, the average age of the patients with CHF was 12 years older than the average age of the patients without CHF (71 years versus 60 years, $p<.0001$). This would confound the results because BNP levels increase with age.

According to the authors, these findings may have an important clinical implication for the diagnosis of CHF in this group of patients. ED physicians were either uncertain or missed the diagnosis of CHF in some of those ultimately proven to have CHF. Given the low rates of use of chronic CHF medications in this group, use of additional diagnostic measures to correctly diagnose CHF can provide a therapeutic opportunity for these patients.

In another subgroup analysis of the multi-centre trial [53], Knudsen et al. compared different circulating BNP levels with chest X-ray findings in the diagnosis of CHF in patients with dyspnea. Eight hundred eighty patients with complete information on BNP levels, historical, clinical, and electrocardiography data, and chest X-ray findings were included in the analysis. The analysis found that BNP measurement and chest X-ray provided complementary diagnostic information beyond that derived from historical and clinical variables. Sensitivity decreased and specificity increased with increasing BNP cut-off values.

According to the authors, clinicians should probably use a low cut-off if the main goal is to exclude the possibility of CHF. Conversely, a relatively high cut-off may be recommended if the goal is to identify patients with a high likelihood of acute CHF. In patients with moderately elevated BNP levels (100 to 300 pg/ml), additional information including that obtained from chest X-ray should be taken into account, and additional tests including an echocardiogram may be required.

Evidence from single centre trials

Morrison et al. [6] reported the results from a single centre study on the utility of the BNP test in differentiating CHF from lung disease in a mostly male population presenting with dyspnea. This study was published in 2002. It was noted that another study, published in 2001 by Dao et al. [58], had the same study objective, study design, inclusion/exclusion criteria, and outcome measurement and was done by the same research group. The only difference is that Dao et al. reported the results from 250 patients, while Morrison et al. reported the results from 321 patients. The correspondent author of these two studies was contacted for further information but no response was obtained. It is most likely that the study by Morrison et al. was an

extension of the study by Dao et al., thus only the results from the Morrison study are presented in this report.

Morrison et al. [6] concluded that BNP was able to distinguish CHF from pulmonary and other clinical presentations with a high specificity, sensitivity and accuracy. Even in those patients with co-morbid conditions of CHF and COPD, BNP was useful in distinguishing the reasons for the visits to EDs. Correlation between BNP levels and age of participants was not reported in this study.

Knudsen et al. [54] assessed the effect of age and gender on the diagnostic accuracy of BNP measurement in 155 consecutive patients presenting with acute dyspnea. They found that the accuracy of a rapid, point-of-care test for BNP is high for the diagnosis of CHF in an unselected patient population with dyspnea. BNP testing tended to be less accurate in the elderly (≥ 76 years), and in women compared to men, although these differences were not statistically significant.

Bayés-Genís et al. [15] evaluated the utility of NT-proBNP in the emergency diagnosis and in-hospital monitoring of patients with acute dyspnea and ventricular dysfunction. Only the findings regarding the diagnostic use of NT-proBNP are presented in this report. The NT-proBNP concentrations in patients with decompensated CHF or masked CHF (defined as CHF clinically difficult to diagnose owing to the presence of pulmonary disease which produced overlapping signs and symptoms) were significantly higher than in the non-cardiac patients or the control group. Correlations between NT-proBNP levels and age and gender of participants were not reported in this study.

According to the authors, a NT-proBNP cut-off value of 115 pmol/l provided an excellent ability to discriminate ventricular dysfunction from subjects with normal cardiac function. However, relying on a single value may limit the test's utility. Using the cut-off value of 115 pmol/l may have some limitations in an acute care setting, since it has a negative predictive value of only 70% to rule out patients with dyspnea and normal heart function. Therefore, both a high and a low cut-off may be desired, a high value (115 pmol/l) for its specificity and positive predictive value, and a low value (30 pmol/l) for its high sensitivity and negative predictive values.

Jose et al. [24] looked at the utility of NT-proBNP in the diagnosis of CHF. Echocardiography was performed in all participants. This study demonstrated that NT-proBNP values were significantly higher in patients with CHF than that in patients with no CHF and increased significantly as the severity of CHF (according to the NYHA functional classification) increased. NT-proBNP levels were also significantly negatively correlated to the LVEF obtained from echocardiography. Correlations between NT-proBNP levels and age or gender of the participants were not reported in this study. The test was performed within three months of sampling and the time

needed to perform the test was not reported. Blinding of clinical judgment to the NT-proBNP results was not reported in the study. The reliability and validity of study findings may thus be questioned.

One study [55] was found that compared the utility of the measurement of three different BNP assays (Biosite and two locally developed BNP assays) and two different NT-proBNP assays (Roche Diagnostic and one locally developed NT-proBNP assay) in the diagnosis of CHF in patients with acute dyspnea. Final diagnosis was determined by two independent cardiologists, who were blinded to the results of the BNP and NT-proBNP assays. Echocardiography was performed in 171 patients out of a total of 205 patients.

The authors found that there were close correlations between all of the five assays. There were significant correlations between age and the results of all five assays. There were inverse correlations between LVEF determined by echocardiography and the results from all of the assays. The correlation between age and BNP/NT-proBNP levels was not significant for all assays among those with CHF, but was significant for all assays among those without CHF ($p<.05$). There were no significant gender differences between BNP/NT-proBNP levels. In general, specificity appeared to be highest with the NT-proBNP assays, although sensitivity was higher with the BNP assays. According to the authors, the Biosite BNP assay may be particularly useful in excluding CHF in the population studied.

One study [56] compared the accuracy of the BNP assay with Doppler echocardiography for the diagnosis of decompensated CHF in patients with acute dyspnea. The final diagnosis was determined by two independent cardiologists and one pneumologist, who were blinded to the results of BNP and Doppler echocardiography. Two groups served as controls, one with no cardiac or pulmonary disease and the other one with chronic stable CHF.

This study found that BNP levels were significantly higher in patients with CHF compared to patients with no CHF or those with stable chronic CHF. Correlations between BNP levels and age or gender of participants were not reported in this study. The most accurate BNP cut-off was 300 pg/ml, while the best negative predictive value was obtained with a BNP cut-off of 80 pg/ml. The authors noted that the BNP assay was of little value when BNP levels were between 80 pg/ml to 300pg/ml, and the BNP assay was also of little value when tests were conducted too soon after the onset of acute dyspnea. In patients with intermediate BNP levels (80 pg/ml to 300 pg/ml), Doppler echocardiography can be used to confirm or rule out CHF.

EXPERT OPINION

Expert opinion was obtained from several cardiologists, a rural family physician, a

pathologist and a clinical chemist in Alberta, Ontario, and British Columbia. According to expert advice, there is currently no validated, standard diagnostic protocol for CHF that clinicians apply in Canada. However there are up-to-date recommendations/ guidelines developed by the Canadian Cardiovascular Society. It was believed that most clinicians would agree that the BNP test is cost effective for the diagnosis of CHF. Laboratories at several British Columbia hospitals have provided BNP on site for diagnostic purposes over the last year. Some clinical investigators use the Biosite BNP assay, while the laboratory platform NT-proBNP is also currently used in British Columbia. Foothills Medical Centre in Calgary is the only centre in Alberta which uses the BNP test routinely. The point-of-care BNP assay is used at the Heart Failure and Heart Transplantation Clinics in Calgary as an adjunct to clinical diagnosis of CHF.

From the perspective of a rural family physician working at the ED, the BNP test would be an interesting supplement to rural ED management. It would clearly supplement currently available clinical evaluation with ECG and chest X-ray. Most of the physicians practicing in rural areas would agree that tools that support local decision making would expedite appropriate treatment, which may or may not require transfer to urban centres. The ability to do the test locally at the point of care would be valuable, since using the more expensive auto analyzer technique requires transport of the patient, or at very least a blood sample, to a central facility. Appropriate education on the role and usefulness of the BNP test is important to rural physicians.

According to a document outlining the consensus reached by a group of Canadian heart failure specialists (personal communication, Dr. Debra Isaac, April 2004), for new patients presenting to the ED with dyspnea, BNP testing should be performed conjointly with thorough history, physical exam, chest X-ray, and ECG. Using the suggested decision cut-point of 100 pg/ml for the BNP point-of-care assay and 125 pg/ml for the NT-proBNP assay appears to improve clinical judgment. If the BNP test levels are below the cut-off value, CHF is unlikely and other causes for dyspnea should be considered. BNP must be used and interpreted in a wider clinical context, taking specific patient characteristics such as age and gender into consideration. In the outpatient setting, BNP may be useful as a rule-out test in new patients presenting with suspected CHF. If the BNP concentrations are raised, these individuals should undergo more comprehensive investigations.

There are several BNP studies ongoing in Canada. One multi-centre RCT, *IMPROVE-CHF Canada*, will involve 1,200 patients with shortness of breath and compare BNP-guided to non-BNP guided management. Diagnostic accuracy, prognostic utility of the BNP test as well as its relation to C-Reactive Protein (CRP) and Troponin T (TNT) levels will also be investigated.

CLINICAL GUIDELINES

The most recent (2002/2003) Canadian Cardiovascular Society consensus guideline update for the diagnosis and management of heart failure [39] recommended that patients who present with dyspnea with unclear but suspected cardiac etiologies may be considered for the measurement of BNP concentrations. The BNP assay will assist with the diagnostic decision of the etiology of dyspnea and its management. According to this guideline, BNP concentration is not a stand-alone test for heart failure and must be used in conjunction with careful clinical evaluation, and in patients with an intermediate pre-test likelihood of heart failure [39]. Provincial guidelines and protocols for the use of BNP for the diagnosis of heart failure in adults presenting in the ED with acute shortness of breath have been developed in British Columbia, Canada (personal communication, Dr. Val Dias, April 2004).

Guidelines for the evaluation and management of chronic heart failure, developed jointly by the American College of Cardiology (ACC)/American Heart Association (AHA) were last updated in 2001 [59]. The ACC/AHA guidelines state that *"... The role of brain natriuretic peptide measurement in the identification and management of patients with symptomatic or asymptomatic left ventricular dysfunction remains to be fully clarified"*. These guidelines were updated before the results from the multi-centre Breathing Not Properly trial [17] were published.

The European Society of Cardiology Task Force for the Diagnosis and Treatment of Chronic Heart Failure recommended in their guidelines that natriuretic peptides, including NT-proBNP, "may be most useful clinically as a rule-out test due to consistent and very high negative predictive values" [60].

DISCUSSIONS

Diagnostic accuracy

The full evaluation of the performance of a diagnostic test involves studying test reliability, diagnostic accuracy, diagnostic and therapeutic impact and the net effect of the test on patient outcomes. Information from a diagnostic test should make a diagnosis certain enough for the expected benefits of treating the patient to outweigh the expected consequences of no treatment.

The optimal cut-off values and their predictive characteristics of BNP/NT-proBNP assays varied considerably across the included studies. Different thresholds will produce different sensitivities (proportion in those with disease who have a positive test results) and specificities (proportion of those without the disease who have a negative test result) as seen in Tables 1 and 2.

The likelihood ratios (LRs) calculated and presented in Tables 1 and 2 indicate by how much a given diagnostic test result will raise or lower the pre-test probability of the

target disorders [61]. A guide for using LRs in clinical practice is as follows [61]:

- Positive LR > 10 or negative LR < 0.1 generate large and often conclusive changes from pre- to posttest probability;
- Positive LR of 5-10 and negative LR of 0.1-0.2 generate moderate shifts in pre- to posttest probability;
- Positive LR of 2-5 and negative LR of 0.2-0.5 generate small (but sometimes important) change in probability;
- Positive LR of 1-2 and negative LR of 0.5-1 alter probability to a small (and rarely important) degree.

Table 1. Summary of calculated LRs for Biosite BNP assay

Study	Participant	Optimal BNP cut-off values (pg/ml)	Sensitivity	Specificity	Positive LR	Negative LR
Maisel et al. [17]	**Age:** mean 64 yrs **Gender:** male 56%	100	90%	76%	3.75	0.13
		50	97%	62%	2.50	0.05
Knusden et al. [54]	**Age:** median 78 yrs (female), 74 yrs (male) **Gender:** male 45%	100 (men)	90%	55.2%	2.00	0.18
		100 (women)	94.3%	54.9%	2.09	0.10
Morrison et al. [6]	**Age:** not available **Gender:** male 95%	94	86%	98%	43	0.14
Lainchbury et al. [55]	**Age:** mean 70 yrs **Gender:** male 49%	208	94%	70%	3.13	0.09
Logeart et al. [56]	**Age:** mean 67 yrs **Gender:** male 67%	300	88%	87%	6.77	0.14
		80	97%	27%	1.33	0.11

As shown in Table 1, among the five studies, only the Logeart et al. study [56] with both positive and negative LRs at a cut-off level of 300 pg/ml seemed to provide reasonably sufficient diagnostic evidence for diagnosing CHF with sufficient accuracy. The positive LR in the large multi-centre study [17] was less than five, suggesting that the cut-off value of 100 pg/ml may provide only minor diagnostic evidence for CHF. The study by Lainchbury et al. [55] and Knusden et al. [54] demonstrated a similar finding. The positive and negative LR in the Morrison study [6] was 43 and 0.14, respectively, which appeared promising. However some issues need to be considered when interpreting these results.

Table 2. Summary of calculated LRs for Roche NT-proBNP assay

Study	Participant	Optimal NT-proBNP cut-off values (pmol/l)	Sensitivity	Specificity	Positive LR	Negative LR
Bayés-Genís et al. [15]	**Age:** mean 70 yrs **Gender:** male 60%	115	91.4%	93.3%	13.64	0.09
		30	98.6%	46.7%	1.85	0.03
Lainchbury et al. [55]	**Age:** mean 70 yrs **Gender:** male 49%	340	80%	87%	6.15	0.23

As indicated in Table 2, among the two studies, only the Bayés-Genís et al. study [15] with both positive and negative LRs at a cut-off level of 115pmol/l seemed to provide strong diagnostic evidence for diagnosing CHF with sufficient accuracy.

It was suggested that, in practice, both a high and a low cut-off values might be used; a high cut-off value for its specificity and positive predictive value and a low cut-off value for its high sensitivity and negative predictive value [44]. However, there was no agreement on such high or low values of BNP or NT-proBNP based on currently available evidence.

Among the included studies, the standard deviations of BNP levels in the different groups are fairly large, so midrange BNP levels are non-specific. Furthermore, diagnostic BNP levels (<100 pg/ml or >300 pg/ml) are likely more common among patients in whom the diagnosis is clinically obvious, and published test characteristic were from a sample that may have included patients with clinically obvious diagnoses [62].

Factors that affect BNP level

Patient characteristics

BNP levels are generally higher in women than men and normal BNP levels increase with age [12, 31, 63, 64]. BNP levels can be elevated in patients with renal dysfunction due to volume overload as well as in patients with lung disease in part because many patients with end-stage pulmonary disorders have concomitant right ventricular dysfunction [12, 65]. Many elderly women with hypertension associated renal impairment but without CHF have BNP levels >200 pg/ml [65]. Thus, variation in patient characteristics such as age, gender, and presence or absence of renal and pulmonary disease may influence BNP levels of sampled populations. In most of the studies included in this report patients with acute myocardial infarction, renal failure or unstable angina were excluded from the study population.

The ideal study sample is a consecutive or randomly selected series of patients recruited from a relevant clinical population that is representative of those seen in the ED. If not,

a bias arises as the study population may not be representative of the spectrum of diseases within which the test will be applied in practice. As well, it is important that the study sample is selected from similar health care settings. The observed sensitivity and specificity will change if the proportionate mix of the spectrum of patients with the disease and those without the disease varies.

One included study [49] used randomized selection of patients, and four studies [15, 54, 56, 57] reported consecutive selection. Patient characteristics were somewhat different in the five studies in Table 1. For example, the average age of the participants in the Lainchbury study [55] was six years older than that in the multi-centre study [17]. More importantly, there was a substantial difference in gender distribution of the participants among the five studies. In the Morrison study [6] 95% of participants were males, while in the other four studies 45% to 67% of the participants were males. This may partly explain the variance in sensitivities and specificities at similar BNP cut-off values between the study by Morrison et al. [6] and the large multi-centre trial by Maisel et al. [17]. The population studied in the Morrison et al trial [6] does not represent the ED population and hence the results of this study cannot be as readily generalized. These results emphasize the need to be aware of both the variability of test performance across different populations and the way in which test characteristics vary depending on the chosen cut-off value [55]. Based on his experience, the first author of the multi-centre study developed an algorithm for the diagnosis of CHF in the ED [32].

It needs to be realized that the goal of measuring BNP is not to distinguish patients with CHF from young healthy people but to distinguish patients with CHF from elderly patients who have multiple cardiovascular risk factors and conditions but do not have CHF. Diagnosis of CHF can be confidently made with very high levels (>300 pg/ml) of BNP. However, any increase in the threshold value of BNP will increases the false negative rate [66].

Reference standard

It is important that the results for the reference test are very close to the truth or else the performance of the experimental test will be poorly estimated. A partial verification bias occurs where not all of the participants undergo the reference investigation due to reasons such as the invasiveness of the test or its cost. This may lead to the numbers of true negative and false negative participants being reduced and the sensitivity being biased upwards and the specificity downwards [67].

Diagnosis of CHF depends on clinical judgment and other diagnostic tests, which makes final determination of CHF somewhat subjective. The majority of the included studies used the Framingham criteria [68] plus other tests including echocardiography to diagnose CHF. However, the final diagnosis was confirmed by echocardiography only in a portion of the patients and the portion of patients whose final diagnosis was

confirmed by echocardiography varied across these studies. These variations may make the estimated sensitivity and specificity of the different studies less comparable and the diagnostic accuracy derived from these studies less reliable.

Comparison of BNP and NT-proBNP assays

The Lainchbury study [55] compared the diagnostic accuracy of Biosite BNP and Roche NT-proBNP assays and suggested that measurement of BNP and NT-proBNP contributes significantly to the ability to diagnose CHF. The Biosite assay has the advantage of point-of-care applicability; however, the commercially available Roche NT-proBNP assay is available through an automated system, which can give rapid turnaround times for results and throughput a large number of samples simultaneously. The clinical application of these and other commercial assays will require further study to avoid confusion resulting from the different hormones measured, different cut-off values suggested for the diagnosis of CHF, differences in precision and the placement of this test within the armamentarium of diagnostic evaluations recommended by the various guidelines.

SUMMARY AND CONCLUSION

The BNP test, as a new diagnostic blood test, has been widely evaluated for its utility in diagnosing CHF in patients with shortness of breath presenting at the ED or GP office. Scientifically sound clinical evidence, however, is still limited.

The highest level of evidence is from a single centre RCT involving 305 patients and a large international multi-centre prospective trial involving 1,586 patients. Other included studies were single centre trials with relatively small numbers of patients (less than 400 patients). Most studies reported blinding of the cardiologists to the results of the BNP test or echocardiography or the clinical judgment of the ED physician, as they were the ones who determined the final diagnosis. Echocardiography, as the gold standard for diagnosing CHF, was not performed in all participants in most of the included studies.

The RCT by Wright et al. [49] demonstrated that NT-proBNP measurement significant improved GP's diagnostic accuracy of CHF by enabling GPs to correctly rule out CHF The BNP test might be a useful addition to the diagnosis of CHF in the primary care setting, as over-diagnosis of CHF by GPs is common. The multi-centre trial showed that in conjunction with other clinical information, rapid BNP measurement is useful in diagnosing or ruling out CHF in the ED population.

The majority of studies included in this report found that average BNP or NT-proBNP levels were significantly higher in patients (mean age 54 years to 72 years) with CHF but without renal disease, acute myocardial infarction or unstable angina compared to patients with no CHF. Some studies found that the BNP level increased as the clinical

severity of CHF increased but the ranges overlapped among the four NYHA classification levels. BNP levels also inversely correlated with LVEF obtained by echocardiography.

It should be noted, however, that BNP concentration is elevated in conditions other than CHF. Plasma BNP concentrations increase normally with age; are higher in females; increase in renal disease, advanced pulmonary disease and in other cardiac conditions; and in those patients on beta blockers, although the multi-centre Breathing Not Properly trial did not find statistically significant differences with Biosite BNP.

When the diagnostic accuracy of the Biosite BNP assay was compared to Doppler echocardiography, it was found that both measures are useful for distinguishing the cause of acute dyspnea. Doppler analysis of the mitral inflow pattern however, was more accurate than the BNP test, particularly in patients with intermediate BNP levels. The diagnostic value of echocardiography for confirming CHF appears to be superior to the BNP test.

It is still early to judge the relative clinical value of the BNP versus NT-proBNP assays for diagnosing the cause of dyspnea. Limited evidence suggests that both assays appear to have comparable diagnostic accuracy and have their own advantages and disadvantages. BNP assays appear to provide additional diagnostic value to clinical judgment in the diagnosis of CHF in patients with acute dyspnea (without renal disease, acute myocardial infarction or unstable angina), especially for ruling out CHF and in EDs where echocardiography is usually not available.

Misdiagnoses of CHF can be life-threatening because treatments for CHF are hazardous to patients with other conditions such as COPD and vice versa. Diagnostic BNP testing is currently provided in some hospitals in Ontario and British Columbia.

It is important to keep in mind that BNP testing is not a stand-alone test and cannot replace any elements of the currently used CHF diagnostic protocols, based on the currently available evidence. The optimal BNP cut-off values, either for establishing the diagnosis of or for ruling out CHF, remain to be determined. Different statements about the value of BNP testing in the American and European Guidelines reflect controversy in using BNP testing for the diagnosis of CHF. Questions regarding the clinical outcomes of adding BNP testing and cost-effectiveness of BNP testing remain to be answered by further research. Research studies are currently underway in Canada.

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Technotes are brief reports, prepared on an urgent basis, which draw on limited reviews and analysis of relevant literature and on expert opinion and regulatory status where appropriate. They are not subject to a formal external review process.

APPENDIX A: METHODOLOGY

Search strategy

Literature searches were conducted by the AHFMR librarian between June 25 and June 29, 2004. Major electronic databases searched include: PubMed, EMBASE, Cochrane Library, Web of Science, NHS Center for Reviews and Dissemination (CRD) databases (NHSEED, HTA, DARE). Various library collections, and web sites of clinical trials, guidelines, regulatory agencies, evidence based resources and other HTA related agencies were searched. Internet search engines were also used to locate grey literature.

Medical Subject Headings (MeSH) Subject Headings related to the topic: Natriuretic Peptide, Brain/Heart Failure, Congestive/left ventricle dysfunction; Heart Failure; Diagnostic Tests, routine; diagnosis. Keywords used included: CHF; BNP, type B; "ventricular dysfunction"; "diagnostic test"; detection, screening, marker and predictor.

Database	Edition	Platform or URL	Search Terms†
Cochrane Library	Searched 2004/06/29	Issue 4, 2003	(Brain natriuretic peptide$ OR BNP OR type B brain natriuretic peptide$)
CRD Databases (DARE, NHS EED, HTA Database)	Searched 2004/06/29	http://agatha.york.ac.uk/welcome.htm	(Brain natriuretic peptide OR BNP OR type B brain natriuretic peptide) AND (Congestive heart failure OR ventricular dysfunction OR CHF OR heart disease)
ECRI: ECRI Full Technology Assessment Report, HTAis, Health Technology Forecast	Searched 2004/06/29	http://www.ecri.org/	(Brain natriuretic peptide OR BNP OR type B brain natriuretic peptide) AND (congestive heart failure OR Congestive Heart Failure/ OR CHF OR ventricle and dysfunction OR heart failure OR Heart Failure)
EMBASE	Searched 2004/06/25	Licensed OVID Search Interface	(brain natriuretic peptide$ OR BNP OR type B Brain Natriuretic Peptide$) AND (congestive heart failure CR Congestive Heart Failure/ OR CHF OR ventricle and dysfunction OR heart failure OR Heart Failure) AND (diagnosis OR diagnostic test$ OR predict$ OR marker OR indicat$)
Web of Science (Science Citation Index)	Searched 2004/06/29	http://www.library.ualberta.ca	TS=(BNP OR brain natriuretic peptide* OR type B brain natriuretic peptide) AND TS=(congestive heart failure OR CHF OR ventricular dysfunction OR heart failure OR heart disease) AND TS=(Diagnos* OR diagnostic test*)

Database	Edition	Platform or URL	Search Terms[†]
CINAHL	Searched 2004/06/29	Licensed Resource 2003	(Brain natriuretic peptide$ OR BNP OR type B brain natriuretic peptide$) AND (congestive heart failure OR CHF OR ventricular dysfunction) AND (Diagnosis OR diagnos$ OR diagnostic test$)
PubMed	Searched 2004/06/29	http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?holding=icauahslib	(Brain natriuretic peptide* OR BNP OR type B brain natriuretic peptide*) AND (congestive heart failure OR CHF OR ventricular dysfunction) AND (Diagnosis OR diagnos* OR diagnostic test* OR indicat* OR detect* OR screen* OR marker* OR predict*) Clinical Queries Diagnosis / sensitivity
TRIP Database	Searched 2004/06/29	Licensed Resource	(Brain natriuretic peptide OR BNP OR type B brain natriuretic peptide)
Bandolier	Searched 2004/06/29	http://www.jr2.ox.ac.uk/bandolier/	BNP OR brain natriuretic peptide OR type B brain natriuretic peptide
CCOHTA	Searched 2004/06/29	http://www.ccohta.ca/entry_e.html	Brain natriuretic peptide OR BNP
AETMIS	Searched 2004/06/29	http://www.aetmis.gouv.qc.ca/en/	Brain natriuretic peptide OR BNP
NICE (Technology Appraisals and Guidelines)	Searched 2004/06/29	http://www.nice.org.uk	Brain natriuretic peptide OR BNP
AMA Guidelines	Searched 2004/06/29	http://www.albertadoctors.org/resources/guideline.html	Brain natriuretic peptide OR BNP
CMA InfoBase	Searched 2004/06/29	http://mdm.ca/cpgsnew/cpgs/	Brain natriuretic peptide OR BNP
National Guideline Clearinghouse	Searched 2004/06/29	http://www.guideline.gov/	Brain natriuretic peptide OR BNP
Alberta Health and Wellness	Searched 2004/06/29	www.health.gov.ab.ca/	Brain natriuretic peptide OR BNP
US Food and Drug Administration Database	Searched 2004/06/29	http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMN/pmn.cfm	Brain natriuretic peptide OR BNP AND diagnosis
US Medicare Coverage Database	Searched 2004/06/29	http://www.cms.gov/coverage/	Brain natriuretic peptide OR BNP
CMA Clinical Practice Guidelines Database	Searched 2004/06/29	http://mdm.ca/cpgsnew/cpgs/index.asp	Brain natriuretic peptide OR BNP

Database	Edition	Platform or URL	Search Terms†
National Guideline Clearinghouse	Searched 2004/06/29	www.guideline.gov	Brain natriuretic peptide OR BNP
CCOHTA	Searched 2004/06/29	http://www.ccohta.ca/publications/pubs_e.asp	Brain natriuretic peptide OR BNP
AETMIS	Searched 2004/06/29	http://www.aetmis.gouv.qc.ca/en/index.php	Brain natriuretic peptide OR BNP
NICE: National Institute for Clinical Excellence (UK NHS)	Searched 2004/06/29	http://www.nice.org.uk/	Brain natriuretic peptide OR BNP
Clinical Trials Database	Searched 2004/06/29	http://www.clinicaltrials.gov/	Brain natriuretic peptide OR BNP AND type B AND Congestive heart failure OR ventricular dysfunction OR CHF
National Research Register (UK Clinical Trials)	Searched 2004/06/29	http://www.update-software.com/nrr/CLIBINET.EXE?A=1&U=1001&P=10001	Brain natriuretic peptide OR BNP AND type B

Notes:
Truncation: * / $ are truncation characters that retrieve all possible suffix variations of the root word e.g. surg* retrieves surgery, surgical, surgeon, etc. Limits: †Searches were limited to English and German language, and publication dates: January 1998 - June 29, 2004

Inclusion criteria

Studies were included if they met all of the following criteria:

- ***Study design:*** systematic reviews (see Cook et al. 1997 [69] for the definition of systematic review), RCTs, non-randomized controlled trials, or prospective studies, published in English from 1998 onwards.
- ***Participants:*** adult patients (sample >50) presenting at the ED or primary care physician office with shortness of breath.
- ***Diagnostic test:*** measurement of blood BNP or NT-proBNP levels for the diagnosis of CHF.
- ***Outcome measurement:*** BNP/NT-proBNP levels in patients with or without CHF; correlation of BNP/NT-proBNP levels with severity of CHF; predictive characteristics including area under ROC curve, sensitivity, specificity, or positive predictive values, negative predictive values, positive LR, negative LR, or odds ratio if available.

Exclusion

Studies were excluded if they focused on:

- Test for monitoring the treatment of CHF;
- Screening test to detect LV systolic dysfunction in the general population or primary health care;
- Prognosis or risk stratification of patients with chronic CHF or other cardiac diseases;
- Diagnosis of LV hypertrophy in hypertensive patients.
- Risk stratification after acute myocardial infarction;
- Biomarker for ventricular remodelling; or
- Cost-effectiveness of using the BNP test.

APPENDIX B: EVIDENCE OF EFFICACY OF BNP TESTING FOR DIAGNOSING CHF

Table B1: Use of BNP in primary care setting

Study	Patients/setting	Source/comparator	Result	Conclusion
Wright et al. 2003 [49] RCT New Zealand **Objective:** to determine the effect of NT-proBNP on the diagnostic accuracy of CHF in primary care.	**Total number:** 305 pts with dyspnea/peripheral edema EG (GP review visit with NT-proBNP results): n = 153 CG (GP review visit without NT-proBNP results): n = 152 **Age:** mean 72 years **Gender:** 35% males **Exclusion:** 1) pts required urgent admission to the hospital or unstable to provide informed consent 2) hospital admission with a diagnosis of CHF 3) echocardiography for assessment of LV function, outpatient cardiologic assessment for the evaluation of dyspnea/edema during the previous 12 months **Setting:** GP office	**NT-proBNP test:** radioimmunoassay (local research) **Reference standard for CHF:** clinical diagnosis was made by a panel of four experts (3 cardiologists and one GP) using the rigorous application of pre-defined criteria. Panel members were independent of all study procedures and were blind to each patient's group allocation and NT-proBNP results. The panel reviewed all clinical data for each pt, including ECG, chest X-ray, and echocardiography (but excluding BNP measurements). The panel decision was based on the European Society of Cardiology Working Group on CHF diagnostic criteria.	**Diagnostic accuracy:** EG: improved 21% (from 49% diagnoses correct to 70%) CG: improved 8% (from 52% diagnoses correct to 59%) (p=.002) **Predictive characteristics:** AUC=0.85 Sensitivity and specificity were maximized at 100 pmol/l (Sensitivity and specificity were only presented in the ROC curve. Two authors of the study were contacted but no more information was obtained).	NT-proBNP measurement significantly improves the diagnostic accuracy of CHF by GPs. The main impact was in enabling GPs to correctly rule out CHF. NT-proBNP is particularly important in decreasing the over-diagnosis of CHF that occurs in primary care setting.

Table B1: Use of BNP in primary care setting (cont'd)

Study	Patients/setting	Source/comparator	Results	Conclusion
Nielsen et al. 2004 [57] Denmark **Objective:** to test the yield of NT-proBNP for detection and exclusion of CHF in a patient population seen in general practice because of dyspnea. This study received some financial support from the manufacturer.	**Total number:** 345 consecutive pts with dyspnea (Oct 1998-Oct 2000) **Age:** median 65 years **Gender:** 51% males **Exclusion:** not available **Setting:** GP office	**NT-proBNP test*:** sandwich immunoassay (EIMA) with 2 antibodies (Roche Diagnostics) **Reference standard for CHF:** final diagnosis was based on a combination of medical history, physical examination, ECG, chest X-ray, lung spirometry, echocardiogram, and blood tests (blood hemoglobin, thyroid hormones, creatinin, sodium, potassium and glucose). * Test was performed Oct 2001.	**NT-proBNP values (pmol/l):** CHF: 189 vs. non-CHF: 17 ($p<.001$) **Predictive characteristics** (from 287 pts aged 50 years or older): ***For Men:*** AUC=0.93 NT-proBNP of 11 pmol/l Sens=96%, Spec=67%, PPV=57%, NPV=97%, PLR=2.9, NLR=0.06 ***For Women:*** AUC=0.90 NT-proBNP of 17 pmol/l Sens=94%, Spec=69%, PPV=48%, NPV=97%, PLR=3.0%, NLR=0.09	CHF cannot be diagnosed or excluded reliably on a clinical basis alone for patients with dyspnea seen in general practice. For patients 50 years or older, CHF could be ruled out with a high probability if the NT-proBNP level in blood did not exceed 11 pmol/l in men and 17 pmol/l in women. Exclusion of dyspnea of cardiac origin by means of a low level of NT-proBNP may make echocardiography redundant in half of the patients who consult their GP because of dyspnea.

AUC: area under the receiver-operating characteristics curve; BNP: B-type natriuretic peptide; CG: control group; CHF: congestive heart failure; ECG: electrocardiogram; EG: experimental group; GP: general practitioner; LV: left ventricular; NLR: negative likelihood ratio; NPV: negative predictive value; NT-proBNP: N-terminal-proBNP; PLR: positive likelihood ratio; PPV: positive predictive value; pts: patients; RCT: randomized controlled trial; Sens: sensitivity; Spec: specificity; vs.: versus

Table B2. Use of BNP in the ED – Evidence form a multi-centre study

Study	Patients/setting	Source/comparator	Result	Conclusion
Maisel et al. 2002 [17] Seven centres from USA, France, Norway **Objective:** to validate and characterize the use of BNP levels in the diagnosis of CHF in a broad population of patients with dyspnea This study received some financial support from the manufacturer.	**Total number:** 1,586 pts with shortness of breath **Age:** mean 64 years **Gender:** 56% males **Exclusion:** 1) age <18 years 2) AMI or renal failure, 3) unstable angina unless their predominant presentation was dyspnea **Setting:** ED	**BNP test:** fluorescence immunoassay kit (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was adjudicated by 2 independent cardiologists, blinded to the BNP results and ED physicians' diagnosis, based on Framingham and NHANES [70] CHF scores, medical history, ECG, chest X-ray, echocardiogram, radionuclide angiography, or left ventriculography.	**BNP values (pg/ml):** Dyspnea due to CHF: 675±450 vs. dyspnea due to non-CHF: 110±225 (p<.001) vs. dyspnea due to non-cardiac cause but with baseline LV dysfunction: 346±390 (p<.001) **Predictive characteristics:** AUC=0.91 BNP of 100 pg/ml Sens=90%, Spec=76%, PPV=79%, NPV=89%, Accuracy=83% BNP of 50pg/ml Sens=97%, Spec=62%, PPV=71%, NPV=96%, Accuracy=79% Logistic-regression analysis: BNP level of 100 pg/ml was the strongest independent predictor of CHF (odds ratio: 29.60) Increased heart size on chest X-ray Accuracy=81% History of CHF Accuracy=75% Rales on physical exam Accuracy=69% History of paroxysmal nocturnal dyspnea Accuracy=60% **BNP values (pg/ml) & clinical severity of CHF** BNP values differed significantly as a function of the severity of CHF (p<.001) 244±286 (NYHA class I) vs. 389±374 (NYHA class II) vs. 640±447 (NYHA class III) vs. 817±435 (NYHA class IV)	Used in conjunction with other clinical information, rapid measurement of BNP is useful in establishing or excluding the diagnosis of CHF in patients with acute dyspnea.

Table B2: Use of BNP in the ED – Evidence form a multi-centre study (cont'd)

Study	Patients/setting	Source/comparator	Result	Conclusion
Maisel et al. 2004 [50] Further analysis of the multi-centre trial [17] **Objective:** to explore the effect of age, race, and gender on BNP decision statistics as well as the impact that changing cut-offs might have on the cost-effectiveness of diagnostic decisions that utilize BNP information.	**Total number:** 1586 pts with shortness of breath **Age*:** mean 64 years **Gender:** 56% males **Exclusion*:** 1) age <18 years 2) AMI or renal failure, 3) unstable angina unless their predominant presentation was dyspnea **Setting*:** ED * from Maisel et al. 2002 [17]	**BNP test:** fluorescence immunoassay (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was based on independent confirmation of 2 cardiologists and was based on the information including history, physical examination, reports of other blood tests, interpretation of chest radiographs, and interpretation of other diagnostic tests.	**BNP values (pg/ml):** CHF: 587 (median) vs. Non-CHF: 34 (median) **Predictive characteristics:** ED probability 50% Sens=74.3%, Spec=81.7% BNP of 100 pg/ml Sens=90.4%, Spec=72.9% BNP of 200 pg/ml Sens=81.4%, Spec=85.1% BNP of 300 pg/ml Sens=72.5%, Spec=88.6% BNP of 400 pg/ml Sens=62.7%, Spec=91.1% **BNP levels & age:** BNP levels increased with increasing age (p<.001) **BNP level & gender:** The difference between men and women was not significant (P=.756) **BNP level & race:** BNP levels higher in Caucasians compared to African Americans ((p<.001)	Both BNP levels and rates of CHF increased with age. Ethnic differences were small but significant, while gender differences were not statistically significant. Higher BNP levels in older subjects result in decreased specificity for a given BNP cut-point. Although BNP levels are known to increase with age, this fact by itself is not sufficient to indicate that higher cut-points should be used for older persons, especially since the prevalence of CHF increases with age as well. If one assumes that failing to treat cases of CHF is worse than treating negative cases, then relatively low BNP cut-points (e.g., ≤100 pg/ml) should be used in patients presenting to the ED with a chief complaint of dyspnea, regardless of age, gender, or ethnicity.

Table B2: Use of BNP in the ED – Evidence form a multi-centre study (cont'd)

Study	Patients/setting	Source/comparator	Result	Conclusion
McCullough et al. 2002 [51] Subgroup analysis of the multi-centre trial [17] **Objective:** to determine the added diagnostic value of BNP over the conventional information obtained in the evaluation of patients with acute dyspnea.	**Total number:** 1,538 pts with dyspnea **Age:** mean 64 years **Gender:** 55.7% males **Exclusion:** 1) advanced renal failure 2) AMI 3) overt cause of dyspnea (chest wall trauma, penetrating lung injury) 4) no ED physician assessment of clinical probability of CHF **Setting:** ED	**BNP test:** fluorescence immunoassay kit (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was adjudicated by 2 independent cardiologists, blinded to the BNP results and ED physicians' diagnosis, based on Framingham and NHANES [70] CHF criteria, medical history, ECG, chest X-ray, echocardiogram, and other clinical tests and consultations.	**Predictive characteristics:** BNP ≥ 100 pg/ml Sens=90%, Spec=73%, PPV=75%, NPV=90%, Accuracy=81.2%, PLR=3.4 Clinical judgment for high (80%-100%) ED probability of CHF Sens=49%, Spec=96%, PPV =91% NPV=68%, Accuracy=74%, PLR=11.5 Composite of clinical judgment and BNP>100 pg/ml Sens=94%, Spec=70%, PPV=74%, NPV =93%, Accuracy=81.5%, PLR=3.2 AUC=0.86 for clinical judgment, 0.90 for BNP, 0.93 for the 2 in combination (p<.001 for all pairwise comparison)	In a multinational sample of men and women seen in the ED with acute dyspnea, BNP measurement would have added to clinical judgment in establishing a final diagnosis of CHF. In those patients with an intermediate probability of CHF, BNP would have clarified the diagnosis in the majority of cases.
McCullough et al. 2003 [52] Subgroup analysis of the multi-centre trial [17] **Objective:** to determine whether BNP can distinguish new-onset CHF in patients with COPD or asthma presenting with dyspnea to the ED.	**Total number:** 417 pts with acute dyspnea **Age:** mean 62 years **Gender:** 60.4% males **Exclusion:** 1) advanced renal failure 2) AMI 3) overt cause of dyspnea (chest wall trauma, penetrating lung injury) **Setting:** ED	**BNP test:** fluorescence immunoassay kit (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was adjudicated by 2 independent cardiologists, blinded to the BNP results and ED physicians' diagnosis, based on Framingham and NHANES [70] CHF scores, medical history, ECG, chest X-ray, echocardiogram, and other clinical tests and consultations.	**BNP values (pg/ml):** CHF: 587.0±426.4 vs. Non-CHF: 108.8±221.3 (p<.0001) **Predictive characteristics:** BNP of 100 pg/ml: Sens=93.1%, Spec=77.3%, PPV=51.9%, NPV=97.7%, Accuracy=80.6%, PLR=4.10, NLR=0.09	Adding BNP testing for patients with a history of asthma or COPD increases the detection of newly diagnosed or previously unrecognized CHF by approximately 20%. This adds a substantial therapeutic opportunity for this group of patients, allowing the initiation and chronic administration of angiotensin-converting enzyme inhibitor and beta-blocker therapy, as well as other CHF management strategies.

Table B2: Use of BNP in the ED – Evidence form a multi-centre study (cont'd)

Study	Patients/setting	Source/comparator	Results	Conclusion
Knudsen et al. 2004 [53] Subgroup analysis of the multi-centre trial [17] **Objective:** to compare chest X-ray findings and circulating BNP levels as adjunct to clinical findings in the diagnosis of CHF patients presenting with acute dyspnea.	**Total number:** 880 pts with acute dyspnea **Age:** mean 64 years **Gender:** 55% males **Exclusion:** 1) dyspnea caused by stabbing injuries, trauma, or pneumothorax 2) AMI or renal failure, **Setting:** ED	**BNP test:** fluorescence immunoassay kit (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was adjudicated by 2 independent cardiologists, blinded to the BNP results and ED physicians' diagnosis, based on Framingham and NHANES [70] CHF scores, medical history, ECG, chest X-ray, echocardiogram, and other clinical tests and consultations.	**BNP values (pg/ml):** CHF: 689±458 vs. Non-CHF: 121.8±249 (p<.0001) **Predictive characteristics:** BNP of 100 pg/ml: Sens=90%, Spec=75%, PLR=3.66, NLR=0.14 Cardiomegaly on x-ray: Sens=79%, Spec=80%, PLR=3.98, NLR=0.26 Cephalization on x-ray: Sens=41%, Spec=96%, PLR=9.41, NLR=0.61 Interstitial edema on x-ray: Sens=27%, Spec=98%, PLR=12.67, NLR=0.72 Alveolar edema on x-ray: Sens=6%, Spec=99%, PLR=7.00, NLR=0.95	BNP measurement and chest X-ray provided complementary diagnostic information beyond that derived from historical and clinical variables. BNP appeared to be the single strongest predictor of the diagnosis of acute CHF, suggesting that BNP measurement should be performed routinely in the patient with acute dyspnea. This study, however, also supports the continued practice of obtaining a detailed history and performing a thorough physical examination and chest X-ray.

AMI: acute myocardial infarction; AUC: area under the receiver-operating characteristics curve; BNP: B-type natriuretic peptide; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; LV: left ventricular; LVEF: left ventricular ejection fraction; NPV: negative predictive value; Pts: patients; CG: control group; ED: emergency department; NYHA class: New York Heart Association functional classification; NHANES: National Health and Nutrition Examination Survey; NLR: negative likelihood ratio; NT-proBNP: N-terminal-proBNP; PLR: positive likelihood ratio; PPV: positive predictive value; r: correlation coefficient; Sens: sensitivity; Spec: specificity; vs.: versus

Table B3: Use of BNP in the ED – Evidence from single-centre studies

Study	Patients/setting	Source/comparator	Results	Conclusion
Morrison et al. 2002 [6] USA **Objective:** to assess whether a rapid assay for BNP levels could accurately differentiate CHF from dyspnea of pulmonary etiologies. This study received some financial support from the manufacturer.	**Total number:** 321 pts with acute dyspnea **Age:** not available **Gender:** 95% males **Exclusion:** 1) Pts whose dyspnea was clearly not secondary to CHF 2) Pts with unstable angina or acute MI unless their predominant presentation was dyspnea. **Setting:** ED	**BNP test:** fluorescence immunoassay (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was based on independent confirmation of 2 cardiologists and was based on Framingham CHF criteria and other information, including hospital course, and the results of echocardiogram, nuclear medicine ejection fractions or left ventriculography.	**BNP values (pg/ml):** CHF: 759±799 vs. pulmonary disease: 61±92 (p<.001) Non-CHF with baseline LV dysfunction: 149±84 **Predictive characteristics:** AUC=0.99 BNP of 94 pg/ml Sens=86%, Spec=98%, PPV=98%, NPV=83%, Accuracy =91% History of CHF Accuracy=79% Heart size & pulmonary venous hypertension on chest X-ray Accuracy=73% & 70% (respectively) Elevated jugular venous pressure Accuracy=70%	The rapid measurement of the BNP concentration appears to be a sensitive and specific test for differentiating patients with CHF from primary pulmonary causes of dyspnea in acute care settings. If further studies validate these findings, it is possible that BNP may prove to be a cost-effective addition to the diagnostic armamentarium of acute physicians.
Knudsen et al. 2004 [54] Norway **Objective:** to assess the diagnostic accuracy of BNP in an unselected, predominantly elderly group of patients admitted to the ED with a principal complaint of shortness of breath and to assess whether the diagnostic accuracy differs according to age and gender.	**Total number:** 155 pts with shortness of breath **Age:** median 78 years for females and 74 years for males **Gender:** 45% males **Exclusion:** 1) pts with chest pain 2) Pts whose dyspnea was clearly not secondary to CHF, such as trauma **Setting:** ED	**BNP test:** fluorescence immunoassay (Triage®, Biosite Diagnostics, San Diego, California) **Reference standard for CHF:** final diagnosis was determined by 2 cardiologists based on medical history, physical exam on admission, in-hospital treatment, routine blood tests (excluding BNP or other natriuretic peptides), the reading of the chest X-ray, ECG, pulmonary function tests, and echocardiography, radionuclide ventriculography, and cardiac catheterisation reports (when available).	**BNP values (pg/ml):** Significantly higher in CHF group than in no CHF group (P<.001, BNP values were only presented in the form of figure) **Predictive characteristics:** ***For men:*** AUC=0.90 BNP of 100 pg/ml Sens=90.0%, Spec=55.2%, PPV=73.5%, NPV=80.0%, Accuracy=75.4% ***For women:*** AUC=0.86 BNP of 100 pg/ml Sens=94.3%, Spec=54.9%, PPV=58.9%, NPV=90.9%, Accuracy =70.9% ***For aged ≥76 year:*** AUC=0.82 ***For aged < 76 years*** AUC=0.88	The accuracy of a rapid point of care test for BNP is high for the diagnosis of CHF in an unselected patient population with acute dyspnea. The results from this study suggest that BNP testing is useful for diagnosing CHF in patients with acute dyspnea presenting to the ED, regardless of age and gender.

Table B3: Use of BNP in the ED – Evidence from single-centre studies (cont'd)

Study	Patients/setting	Source/comparator	Result	Conclusion
Bayés-Genis et al. 2004 [15] Spain **Objective:** to determine the utility of NT-proBNP for the diagnosis of ventricular dysfunction in patients attending the ED for acute dyspnea. This study received some financial support from the manufacturer.	**Total number:** 89 consecutive pts with acute dyspnea **Age:** mean 70 years **Gender:** 60% males **Exclusion:** 1) NYHA I and II 2) age under 40 years 3) dyspnea secondary to chest trauma or cardiac tamponade 4) acute coronary syndrome 5) severe renal insufficiency or liver cirrhosis **Setting:** ED	**NT-proBNP test:** Electrochemiluminescence immunoassay on an Elecsys 1010 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) **Reference standard for CHF:** final diagnosis was adjudicated by 2 cardiologists, blinded to the NT-proBNP results and ED diagnosis, based on medical history, physical examination, ECG, chest X-ray, echocardiogram, spirometry, pulmonary volumes and arterial blood gases.	**NT-proBNP values (pmol/l):** Decompensated CHF: 920±140 and masked CHF: 978±363 vs. non-CHF: 50±15 (p<.01) vs. normal control: 9±3 (p<.001) **Predictive characteristics:** AUC=0.957 NT-proBNP of 115 pmol/l Sens=91.4%, Spec=93.3%, PPV=98.8%, NPV=70%, Accuracy=91.8% NT-proBNP of 30 pmol/l Sens=98.6%, Spec=46.7%, PPV=89.7%, NPV=100%, Accuracy=90.6% Logistic-regression analysis: NT-proBNP level of 115 pmol/l was the strongest independent predictor of ventricular dysfunction (odds ratio: 45.4)	A cut-off value of 115 pmol/l appeared useful to rule-in dyspnea of cardiac origin, and a cut-off value of 30 pmol/l appeared useful to rule-out the cardiac origin of the dyspnea. NT-proBNP is a new candidate marker for the exclusion and detection of ventricular dysfunction, clinically evident or masked, in patients attending the ED for dyspnea.
Jose et al. 2003 [24] India Objective: to evaluate the utility of plasma NT-proBNP for the diagnosis CHF in patients presenting with dyspnea.	**Total number:** 119 pts with shortness of breath **Age:** mean 54 years **Gender:** 65.5% males **Exclusion:** acute coronary syndrome **Setting:** ED or outpatient department **Control:** 86 subjects (mean age 57 years, 60% female) without dyspnea, no known cardiovascular risk factors and no clinical evidence of heart or lung disease.	**NT-proBNP test:** competitive enzyme immunoassay using a Biomedica kit **Reference standard for CHF:** final diagnosis was based on the Framingham criteria and echocardiography.	**NT-proBNP values (pmol/l):** CHF: 389±148 vs. non-CHF: 142±54 (p<.001) **NT-proBNP values (pmol/l) &. clinical severity of CHF:** 261±34 (NYHA class I) vs. 300±161 (NYHA class II) vs. 427±103 (NYHA class III) vs. 528±170 (NYHA class IV) NT-proBNP values increase significantly as the functional severity of CHF increases (p<.001) **NT-proBNP values (pmol/l) & LVEF:** LVEF<40%: 406±152 vs. LVEF>40%: 171±83 There was a significant negative correlation between plasma NT-proBNP and LVEF (r=-.69; p<.001). **Predictive characteristics:** AUC=0.94 NT-proBNP of 200 pol/l Sens=97%, Spec=89%, Accuracy=93%	Plasma NT-proBNP is a sensitive indicator of cardiac dysfunction. The results suggest that NT-proBNP level can be used reliably for the diagnosis of CHF in an outpatient setting. The results demonstrate that measurement of NT-proBNP levels will improve the ability of clinicians to differentiate between patients with shortness of breath due to CHF from those patients who have dyspnea due to other causes.

Table B3: Use of BNP in the ED – Evidence from single-centre studies (cont'd)

Study	Patients/setting	Source/comparator	Results	Conclusion
Lainchbury et al. 2003 [53] New Zealand **Objective:** to compare the utility of BNP (point of care test) and NT-proBNP (commercially available automated assay) in the diagnosis of CHF patients with acute shortness of breath, and to compare these assays with locally developed, well-validated radioimmunoassay for BNP and NT-proBNP. This study received some financial support from the manufacturer.	**Total number:** 205 pts with acute dyspnea **Age:** mean 70 years **Gender:** 49% males **Exclusion:** not available **Setting:** ED	**BNP test:** 1) fluorescence immunoassay (Biosite Diagnostics, San Diego, California) 2) Locally developed radioimmunoassay for Clinical BNP and Research BNP **NT-proBNP test:** 1) Roche Diagnostics NT-proBNP assay, Basel, Switzerland 2) Locally developed radioimmunoassay for NT-proBNP **Reference standard for CHF:** final diagnosis was adjudicated by 2 cardiologists, blinded to BNP results, based on Framingham criteria, medical history, chest X-ray, and echocardiogram.	**BNP/NT-proBNP values:** For all assays, pts with CHF had significantly higher levels ($p<.001$ for all) **Correlations between five assays:** r = 0.902 for Biosite BNP vs. Roche NT-proBNP r = 0.969 for Roche NT-proBNP vs. local NT-proBNP r = 0.911 for Biosite BNP vs. Clinical BNP assay r = 0.916 for Biosite BNP vs. Research BNP assay **Predictive characteristics:** Biosite BNP of 208 pg/ml AUC=0.89 Sens=94%, Spec=70%, PPV=61%, NPV=96%, Accuracy=78% Roche NT-proBNP of 340 pmol/l AUC=0.89 Sens=80%, Spec=87%, PPV=76%, NPV=89%, Accuracy=85%	Results support the use of BNP and NT-proBNP measurement in the assessment of patients with shortness of breath. The commercially available assays compare favorably with well-validated laboratory assays. The Biosite assay may be most useful in excluding CHF in this population, a useful characteristic in a point-of-care test. NT-proBNP assays appear to have somewhat better specificity and positive predictive value.

Table B3: Use of BNP in the ED – Evidence from single-centre studies (cont'd)

Study	Patients/setting	Source/comparator	Results	Conclusion
Logeart et al. 2002 [56] France **Objective:** to compare the accuracy of BNP assay with Doppler echocardiography for the diagnosis of decompensated CHF in patients with acute dyspnea.	**Total number:** 163 pts with severe dyspnea **Age:** mean 67 years **Gender:** 67% males **Exclusion:** 1) AMI 2) chest injury 3) recent surgery **Setting:** ED **Two additional control groups:** ***Normal control:*** 30 pts (65 years or older) with no cardiac or pulmonary disease and no history of hypertension or diabetes mellitus. ***Stable chronic CHF:*** 30 outpatients with chronic stable CHF	**BNP test:** Fluorescence immunoassay (Biosite Diagnostics, San Diego, California) **Doppler echocardiography:** Hewlett-Packard Sonos 1500 (Andover, Massachusetts) machine equipped with a 2.5-MHz probe **Reference standard for CHF**: final diagnosis was determined by 2 cardiologists and one pneumologist, blinded to the results of BNP assay and Doppler echocardiography obtained on admission, based on Framingham criteria and information including hospital course and results of Doppler echocardiography, cardiac catheterization, radionuclide ventriculography, and pulmonary functional tests.	**BNP values (pg/ml):** Acute CHF: 1,022±742 (significantly higher than other groups, p<.001) vs. non-CHF groups: 187±158 vs. Normal control: 44±39 vs. Stable chronic CHF: 144±142 **Predictive characteristics:** ***BNP test*** BNP of 300 pg/ml Sens=88%, Spec=87%, PPV=94%, NPV=75%, Accuracy=88% BNP of 80 pg/ml Sens=97%, Spec=27%, PPV=76%, NPV=93%, Accuracy=78% ***Doppler echocardiography*** LVEF < 0.45 Sens=65%, Spec=85%, PPV=51%, NPV=91%, Accuracy=71% "Restrictive" mitral pattern Sens=89%, Spec=93%, PPV=96%, NPV=80%, Accuracy=91%	Bedside BNP assay and Doppler echocardiography are both useful for establishing the cause of acute dyspnea. Bedside BNP is simple and repeatable. However, Doppler analysis of the mitral inflow pattern was more accurate, particularly in patients with intermediate BNP levels or "flash" pulmonary edema, but was not feasible in 15% of patients. In patients with intermediate BNP level (80 to 300 pg/ml) Doppler echocardiography can be used to confirm or rule out CHF.

AMI: acute myocardial infarction; AUC: area under the receiver-operating characteristics curve; BNP: B-type natriuretic peptide; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; LV: left ventricular; LVEF: left ventricular ejection fraction; NPV: negative predictive value; Pts: patients; CG: control group; ED: emergency department; NYHA class: New York Heart Association functional classification; NHANES: National Health and Nutrition Examination Survey; NLR: negative likelihood ratio; NT-proBNP: N-terminal-proBNP; PLR: positive likelihood ratio; PPV: positive predictive value; r: correlation coefficient; Sens: sensitivity; Spec: specificity; vs.: versus

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